Doc Code: AP.PRE.REQ

PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) SOLOMON2B.2	
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 14550, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on _____ Signature _____ Typed or printed name _____	Application Number 10/749,522	Filed January 2, 2004
	First Named Inventor Beka SOLOMON	
	Art Unit 1649	Examiner K. A. Ballard

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney of record.
Registration number 25,618.

☐ attorney or agent acting under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34 _____

/rlb/
Signature

Roger L. Browdy
Typed or Printed Name

202-628-5197
Telephone number

October 12, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

REASONS WHY REVIEW IS REQUESTED

In the advisory action of October 3, 2007, the examiner stated that the evidence presented with applicant's response after Final Rejection, dated September 12, 2007, would be entered. Claims 7-11 and 25-34 remain rejected. Claims 1-6 have been withdrawn from consideration. No amendments were presented after Final Rejection. The examiner's attempt to rely on a new reference in the Advisory Action is inequitable and should not be permitted.

Briefly, the present invention relates to a pharmaceutical composition comprising a filamentous bacteriophage. The bacteriophage of the composition consists of a filamentous bacteriophage that displays an antibody or an antigen-binding fragment thereof. The antibody or fragment binds to an epitope of β-amyloid so as to inhibit aggregation or cause disaggregation of β-amyloid aggregate when administered to a subject. The filamentous bacteriophage may be part of a composition with a carrier. In a preferred embodiment, the filamentous bacteriophage is an active ingredient of a pharmaceutical composition with a pharmaceutically acceptable carrier. While use of antibodies to an epitope of β-amyloid to inhibit aggregation or cause disaggregation of β-amyloid aggregate is generally known in the prior art, the use of filamentous phage to display such an antibody, or antigen binding fraction, is an improvement over the prior art because it has unexpected properties not suggested by the prior art. Unexpectedly, if administered properly, i.e., intranasally, the filamentous phage will by-pass the blood-brain barrier and carry the antibody directly into the brain where the antibody may find its antigen and cause inhibition of aggregation of β-amyloid or cause disaggregation of β-amyloid aggregate. Thus, the compositions of the present invention have the particularly advantageous property of allowing an antibody to be carried directly to the brain when properly administered. This unexpected property rebuts any *prima facie* case of obviousness the examiner may establish.

Claims 7-11 and 25-34 have been rejected under 35 U.S.C. 103 as being unpatentable over Solomon and Hanan, both as evidenced by Frenkel, and both in view of Prusiner and Pasqualini. The examiner states that Solomon and Hanan teach the inhibition and disaggregation of β-amyloid peptide by monoclonal antibodies and that Frenkel shows the N-terminal EFRH sequence as the

specific anti-aggregating epitope. The examiner states that Hanan indicates that a suitable dlivery system may be developed. Neither Solomon nor Hanan teach compositions comprising filamentous bacteriophage that displays an antibody or epitope binding fragment thereof.

The examiner states that Prusiner teaches methodologies for producing a variety of different prion protein antibodies using combinatorial phage display antibody library technology, i.e., antibodies displayed on filamentous phage. Prusiner teaches that combinatorial antibody library technology is advantageous over traditional hybridoma methodologies for the generation of monoclonal antibodies. The examiner states that Pasqualini teaches the targeting of specific tissues, such as brain, with phage peptide libraries and that this method may provide a new means for selective targeting of therapies. The examiner concludes that Pasqualini teaches that such technology may be used for selective tissue targeting, such as targeting of therapeutic molecules to the brain. Accordingly, the examiner concludes that the artisan would be motivated to produce a filamentous phage displaying an antibody or antigen-binding fragment directed against the anti-aggregating epitope of β-amyloid peptide for potential use in therapeutic applications. The examiner states that such a combination would be met with an expectation of success by the artisan based upon the well established methodology of expressing antibodies or antibody binding fragments on the surface of bacteriophages, as in the construction of phage display libraries. The examiner states that a statement of indended use in the preamble of a claim must be disregarded if the prior art structure is capable of performing the intended use. The examiner states that the skilled artisan would be motivated to develop suitable delivery systems and would recognize the teachings of Prusiner and Pasqualini in this regard. The examiner states that Pasqualini evidences that a combination of a binding fragment region of an antibody and a phage would be a suitable pharmaceutical composition for *in vivo* administration and therefore would not be incongruous with either therapeutic or diagnostic use of the composition. This rejection is respectfully traversed.

There are two reasons why the present rejection should be withdrawn. First, the examiner has not established a *prima facie* case of obviousness. Second, even if the examiner has established a *prima facie* case of obviousness, it has been rebutted by the evidence of record.

No *Prima Facia* Case of Obviousness

In the present case, a person of ordinary skill in the art having common sense at the time of the invention would not have reasonably looked to Prusiner or Pasqualini to solve a problem of antibody delivery to the brain, particularly in view of the fact that neither Prusiner nor Pasqualini are related to antibody delivery. Pasqualini does not use filamentous phage as a "delivery system." Pasqualini uses the phage as a means to generate a random peptide library. He administers the phage rather than the peptides that are displayed on the phage because it would just be too difficult to remove all the peptides before administering them. Pasqualini nowhere suggests that administering the phage provides any delivery advantages. What common sense reason would one of ordinary skill in the art reading Solomon and Hanan have to take the antibody disclosed therein and specially create a phage displaying that antibody, or an epitope binding fraction thereof, solely for the purpose of using that phage as a delivery vehicle? To do so would violate the common sense of the person of ordinary skill in the art, which the Supreme Court says must be looked to when making an obviousness determination. See *KSR International v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007).

Phage is used by Pasqualini by accident because he happened to use phage display technology in order to create his library of peptides. One does not need a library of peptides to practice the invention of Solomon and Hanan. One would need some other reason to put the epitope binding fragment of the antibody of Solomon and Hanan onto a phage. Pasqualini does not teach any advantage of doing so. Pasqualini does not teach that displaying an antibody on a phage will cause selective tissue targeting to the brain. All that Pasqualini teaches is that some tiny fraction of the entire library administered finds it way to the brain and binds to brain tissue. Indeed, Pasqualini only shows that a small amount of phage goes to the brain as compared to the kidney and the liver.

The reason the examiner relies on Prusiner is for its teaching that combinatorial antibody library technology is advantageous over traditional hyridoma methodologies for the generation of monoclonal antibodies. However, the antibody of the primary references has already been obtained by hybridoma technology. Why then would one want to take that antibody and put it on a phage, as the examiner proposes in his combination of references? The only reason to do so is by a

concerted hindsight reconstruction of the present invention, which the Supreme Court has warned is inappropriate.

Any *Prima Facie* Case of Obviousness Has Been Rebutted

An important recent Federal Circuit case is very relevant to the present situation. In *In re Sullivan*, 2007 U.S. App. LEXIS 20600, Fed Cir, Aug. 29, 2007 (copy attached), the Court stated:

> Our predecessor court held that that intended use for the known composition could not render the claim patentable. In this case, applicant does not concede that the only distinguishing factor of its composition is the statement of intended use and, in fact, extensively argues that its claimed composition exhibits the unexpected property of neutralizing the lethality of rattlesnake venom while reducing the occurrence of adverse immune reactions in humans. Such a use and unexpected property cannot be ignored. See *In re Papesch*, 315 F.2d 381, 391, 50 C.C.P.A. 1084, 1963 Dec. Comm'r Pat. 334 (CCPA 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. . . . There is no basis in law for ignoring any property in making such a comparison."). The issue here is not whether a claim recites a new use, but whether the subject matter of the claim possesses an un-expected use. That unexpected property is relevant, and thus the declarations describing it should have been considered by the Board.

The statement in the present claims about inhibiting aggregation or causing disaggregation in the brain of a subject when using the composition of the present invention is an unexpected property that cannot be ignored. The evidence of record establishes the unexpected property of the claimed composition and that the art would teach away from the combination. Pasqualini itself, in the paragraph bridging the two columns thereof states that the blood brain barrier would deter the phage. This teaches away from creating a phage specifically displaying only the antibodies disclosed by Solomon and Hanan. The discovery of the unexpected property that, when administered properly filamentous phage can by-pass the blood-brain barrier and efficiently carry anything displayed thereby to the brain (see examples 7 and 8 of the present specification), is an unexpected property that cannot be ignored when considering whether or not a *prima facie* case of obviousness has been rebutted.

Furthermore, another reason why a person of ordinary skill in the art, using common sense, would not be motivated to use, and indeed would be taught away from using, phage as a delivery vehicle for an antibody is because phage is known to be immunogenic and to increase the immunogenicity of any peptide carried thereby. . See Delmastro et al., "Immunogenicity of Filamentous Phage Displaying Peptide Mimotopes After Oral Administration", *Vaccine*, 15:1276-1285 (1997), of record. This is particularly true when the phage is administered i.v., as is done by Pasqualini. When administering antibodies, no immunological response is desired. The present invention is not a vaccine where it is desirable to raise an immune response to a peptide; it is a delivery vehicle for antibody-binding fragments that bind to anti-aggregating epitopes of Aβ. This is further rebuttal evidence that teaches away from combining Solomon with either Pasqualini or Prusiner. Far from suggesting a desirable delivery system to the brain, those of ordinary skill in the art would understand that it would be an undesirable delivery system and common sense, in combination with the evidence of record, would teach away from doing so. There is nothing in the prior art of record that would lead one of ordinary skill in the art to believe that the use of phage will help the antibody get to the brain. Only the present invention discloses this unexpected property when filamentous phage is administered intranasally, bypassing the blood-brain barrier, as discussed above.

Any discussion in Delmastro about immunogenicity upon intranasal administration is irrelevant to the obviousness determination. The fact remains that those of ordinary skill in the art would not be motivated to use filamentous phage as an antibody delivery system when immunogenicity is to be avoided.

The examiner's attempt to rely on new evidence in an advisory action after prosecution has closed is inappropriate. Prosecution should be reopened and the new art officially applied in the rejection if it is to be considered. Otherwise, applicant has not opportunity to comment on the newly cited art prior to appeal.

Accordingly, for the reasons discussed above, it is urged that this rejection be withdrawn following a pre-brief appeal conference and that this application be passed to allowance.